DECISION

No. 14/22.04.2013

on approval of the Guideline on Good Pharmacovigilance Practices – Annex I - Definitions

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 158/18.02.2013, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 22.04.2013, in accordance with Article 12(5) of Government Decision no. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Sole article. – The Guideline on Good Pharmacovigilance Practices – Annex I – Definitions is approved, in accordance with the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 14/22.04.2013

GUIDELINE ON GOOD PHARMACOVIGILANCE PRACTICES (GFP) Rev.1

Date of entry into force: December 2012

ANNEX I - DEFINITIONS

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Abuse of a medicinal product
Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [Art. 695 (15) of Law 95/2006, as amended].

Advanced therapy medicinal product (ATMP)
A medicinal product for human use that is either a gene therapy medicinal product, a somatic cell therapy product or a tissue engineered products as defined in provisions of Art. 2 (1) a) of (EC) Regulation 1394/2007.

Adverse event (AE); synonym: Adverse experience
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment [Art. 21(m) of Order of the Minister of Health no. 904/25.07.2006 on approval of rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use].
An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect
A response to a medicinal product which is noxious and unintended [Art. 695 (10) of Law 95/2006, as amended][1].
Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline).
Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [Art. 812 (1) of Law 95/2006, as amended]. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.
See also ***Adverse event, Serious adverse reaction, Unexpected adverse reaction, Off-label use, Overdose, Misuse of a medicinal product, Abuse of a medicinal product, Occupational exposure to a medicinal product***

[1] In the context of clinical trials, an adverse reaction is defined as all untoward and unintended responses to an investigational medicinal product related to any dose administered [Art. 2(n) of Directive 2001/20/EC].

Audit
A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled (see ISO 19011 (3.1)[2]).

Audit finding(s)
Results of the evaluation of the collected audit evidence against audit criteria (see ISO 19011 (3.4)[2]).
Audit evidence is necessary to support the auditor's results of the evaluation, i.e. the auditor's opinion and report; it is cumulative in nature and is primarily obtained from audit procedures performed during the course of the audit.
See also ***Audit***

Audit plan
Description of activities and arrangement for an individual audit (see ISO19011 (3.12)[3]]
See also ***Audit***

Audit programme
Set of one or more audits planned for a specific timeframe and directed towards a specific purpose (see ISO 19011 (3.11)[4])
See also ***Audit***

Audit recommendation
Describes the course of action management might consider to rectify conditions that have gone awry, and to mitigate weaknesses in systems of management control (see Sawyer LB et al, 20036).
Audit recommendations should be positive and as specific as possible. They should also identify who is to act on them (Sawyer LB et al, 2003).
See also ***Audit***

Clinical trial
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more Member State [Art. 21 a) of Order of the Minister of Public Health no. 904/2006].
See also ***Ongoing clinical trial, Completed clinical trial, Investigational medicinal product***

Closed signal
In periodic benefit-risk evaluation reports, a signal for which an evaluation was completed during the reporting interval (see Annex IV, ICH- E2C(R2) Guideline).
This definition is also applicable to periodic safety update reports.
See also **Signal**

Company core data sheet (CCDS)

[2] International Organisation for Standardisation (ISO); www.iso.org
[3] The International Organisation for Standardisation (ISO); www.iso.org
[4] The International Organisation for Standardisation (ISO); www.iso.org

For medicinal products, a document prepared by the marketing authorisation holder (MAH) containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product (see Annex IV, ICH-E2C(R2) Guideline).
See also Company core safety information

Company core safety information (CCSI)
For medicinal products, all relevant safety information contained in the company core data sheet prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification (see Annex IV, ICH-E2C(R2) Guideline).
It is the reference information by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Company core data sheet***

Compassionate use of a medicinal product
Making a medicinal product available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product (the medicinal product concerned must either be subject of an application for a central marketing authorisation or must be undergoing clinical trials) [Art. 83 (2) of Regulation (EC) 726/2004].

Completed clinical trial
Study for which a final clinical study report is available (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
See also Clinical trial

Consumer
For the purpose of reporting cases of suspected adverse reactions, a person who is not a healthcare professional such as a patient, lawyer, friend or relative/parent/child of a patient (see Annex IV, ICH-E2D Guideline).

Data lock point
For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR.
For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date (see Annex IV, ICH-E2C(R2) Guideline).
For a development safety update report (DSUR), the date designated as the cut-off date for data to be included in a DSUR, based on the development international birth date (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
Date includes day and month (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
See also ***Periodic safety update report, Development safety update report, International birth date, Development international birth date***

Development international birth date (DIBD)

Date of first approval (or authorisation) for conducting an interventional clinical trial in any country (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

Development safety update report (DSUR)
Format and content for periodic reporting on drugs under development (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

EU reference date; synonym: Union reference date
For medicinal products containing the same active substance or the same combination of active substances, the date of the first marketing authorisation in the EU of a medicinal product containing that active substance or that combination of active substances; or if this date cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances [Art. 819^{3} (5) of Law 95/2006, as amended].

Generic medicinal product
A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies (Art. 704 (2) b) of Law 95/2006, as amended).

Good pharmacovigilance practices (GVP) for the European Union
A set of guidelines for the conduct of pharmacovigilance in the EU, drawn up based on art. 820^{1} of Law 95/2006, as amended, by the European Medicines Agency in cooperation with competent authorities in Member States and interested parties, and applying to Marketing Authorisation Holders in the EU, the Agency and competent authorities in Member States.

Healthcare professional
For the purposes of reporting suspected adverse reactions, healthcare professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners (see Annex IV, ICH-E2D Guideline).

Herbal medicinal product
Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations [Art. 695 (31) of Law 95/2006, as amended].
Herbal substances are all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binominal system [Art. 695 (32) of Law 95/2006, as amended].
Herbal preparations are preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates [Art. 695 (33) of Law 95/2006, as amended].

Homeopathic medicinal product

Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in EU Member States. A homeopathic medicinal product may contain a number of active principles (Art. 695 (4) of Law 95/2006, as amended).

Identified risk
An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
Examples include:
 an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;

 an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group on a parameter of interest suggests a causal relationship;

 an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

In a clinical trial, the comparator may be placebo, an active substance or non-exposure.
Adverse reactions included in section 4.8 of the summary of product characteristics (SmPC) are also considered identified risks, unless they are class-related reactions which are mentioned in the SmPC but which are not specifically described as occurring with this product (these would normally be considered as a potential risk)).
See also ***Risks related to use of a medicinal product, Important identified risk and Important potential risk, Important missing information, Unexpected adverse reaction***

Illegal purposes
See ***Misuse for illegal purposes***.

Immunological medicinal product
Any medicinal product consisting of vaccines, toxins, serums or allergen products:

a) Vaccines, toxins and serums shall cover in particular agents used to produce active immunity (such as cholera vaccine, BCG, polio vaccine, smallpox vaccine);
b) Agents used to diagnose the state of immunity (including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin);
c) Agents used to produce passive immunity (such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin).

Allergen products shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent [Art. 695 (3) of Law 95/2006, as amended].

Important identified risk and important potential risk
An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Risk-benefit balance, Identified risk, Potential risk, Safety concern***

Important missing information
Critical gaps in knowledge for specific safety issues or populations that use the marketed product (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Missing information, Safety concern***

Important potential risk
See ***Important identified risk*** *and* ***Important potential risk***

Individual case safety report (ICSR); synonym: Adverse (drug) reaction report
Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time[5].
See also ***Minimum criteria for reporting***

International birth date (IBD)
The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world (see Annex IV, ICH-E2C(R2) Guideline).

Investigational drug
Experimental product under study or development. This term is more specific than investigational medicinal product, which includes comparators and placebos (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
See also ***Investigational medicinal product***

Investigational medicinal product
An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form [Art. 21 d) of Order of the Minister of Health no. 904/2006].
See also ***Clinical trial***

Labelling
Information on the immediate or outer packaging [Art. 695 (25) of Law 95/2006, as amended].

Medicinal product
Any substance or combination of substances:
 presented as having properties for treating or preventing disease in human beings; or

 which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological

[5] In the context of clinical trials, an individual case is an information provided by a primary source to describe suspected unexpected serious adverse reactions related to the administration of one or more investigational medicinal products to an individual patient at a particular point of time.

or metabolic action, or to making a medical diagnosis [art. 695 (1) of Law 95/2006, as amended].

Medicinal product derived from human blood or human plasma
Any medicinal product based on blood constituents which is prepared industrially by a public or private establishment, such as a medicinal product including, in particular, albumin, coagulating factor(s) and immunoglobulin(s) of human origin [art. 695 (9) of Law 95/2006, as amended].

Minimum criteria for reporting
For the purpose of reporting cases of suspected adverse reactions, the minimum data elements for a case are: an identifiable reporter, an identifiable patient, an adverse reaction and a suspect medicinal product (see Annex IV, ICH-E2D Guideline).
For the purpose of validation of individual case safety reports as qualifying for reporting in the EU, see Module VI.
*See also I**ndividual case safety report***

Missing information
Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.
Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use.
*See also **Off-label use***

Misuse of a medicinal product
Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information.
*See also **Misuse of a medicinal product for illegal purposes***

Misuse of a medicinal product for illegal purposes
Misuse for illegal purposes is misuse with the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault.
*See also **Misuse of a medicinal product***

Name of the medicinal product
The name which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder [Art. 695 (20) of Law no. 95/2006, as amended].
The common name is the international non-proprietary name (INN) recommended by the World Health Organization (WHO), or, if one does not exist, the usual common name [Art. 695 (21) of Law no. 95/2006, as amended].
The complete name of the medicinal product is the name of the medicinal product followed by the strength and pharmaceutical form.

Newly identified signal
In periodic benefit-risk evaluation reports, a signal first identified during the reporting interval, prompting further actions or evaluation

(see Annex IV, ICH-E2C(R2) Guideline).
This definition could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation (see Annex IV, ICH-E2C(R2) Guideline).
This definition is also applicable to periodic safety update reports.
See also **Signal, Closed signal**

Non-interventional trial; synonym: Non-interventional study
A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation; the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; no additional diagnostic or monitoring procedures is applied to the patients and epidemiological methods is used for the analysis of collected data [Art. 21 (c) of Order of the Minister of Public Health no. 904/2006].
Thus, a trial is non-interventional if the following requirements are cumulatively fulfilled:
- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data (see Volume 10 of the Rules Governing Medicinal Products in the EU, Questions & Answers, Version 10.0).

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives.
Non-interventional studies include database research or review of records where all the events of interest have already happened (this may include case-control, cross-sectional, cohort and other study designs making secondary use of data). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met. In these studies, interviews, questionnaires and blood samples may be performed as normal clinical practice. Non-interventional trials do not fall in the scope of Order of the Minister of Public Health no. 904/2006.

Occupational exposure to a medicinal product
For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.

Off-label use
Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.

Ongoing clinical trial
Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
*See also **Clinical trial, Completed clinical trial***

Ongoing signal

In periodic benefit-risk evaluation reports, a signal that remains under evaluation at the data lock point (see Annex IV, ICH-E2C(R2) Guideline).
This definition is also applicable to periodic safety update reports.
See also **Signal, Data lock point**

Overdose
Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

Package leaflet
A leaflet containing information for the user which accompanies the medicinal product [Art. 695 (26) of Law 95/2006, as amended].

Periodic safety update report (PSUR)
Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.
In the EU, periodic safety update reports should follow the format described in Module VII.

Pharmacovigilance
Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem (see WHO[6]).
In line with this general definition, underlying objectives of pharmacovigilance in accordance with the applicable EU legislation for are:
 preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and

 promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

Pharmacovigilance system
A system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Section X of Law 95/2006 and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [Art. 695 (28^1) c) of Law 95/2006, as amended].
In general, a pharmacovigilance system is a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

Pharmacovigilance system master file (PSMF)

[6] World Health Organisation (WHO) "The importance of pharmacovigilance: safety monitoring of medicinal products", Geneva, WHO; 2002.

A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products [Art. 695 point 28^1 d) of Law 95/2006, as amended].
See also ***Pharmacovigilance system***

Post-authorisation safety study (PASS)
Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures [Art. 695 (14) of Law 95/2006, as amended]. A post-authorisation safety study may be an interventional clinical trial or may follow an observational, non-interventional study design.
See also ***Clinical trial, Non-interventional trial***

Potential risk
An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).
Examples include:
 non-clinical toxicological findings that have not been observed or resolved in clinical studies;
 adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship;
 a signal arising from a spontaneous adverse reaction reporting system;
 an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

See also ***Adverse event, Signal***

Quality adherence
Carrying out tasks and responsibilities in accordance with quality requirements [IR Art. 8(3)]
See also ***Quality requirements***

Quality assurance
See ***Quality control and assurance***

Quality control and assurance
Monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out [IR Art 8(3) of Enforcment Regulation (ER) 520/2012].
This applies for the purpose of fulfilling quality requirements.
See also Quality requirements

Quality improvements
Correcting and improving the structures and processes where necessary [IR 520/2012 - Art 8(3)].
This applies for the purpose of fulfilling quality requirements.
See also ***Quality requirements***

Quality objectives
Performance of tasks and responsibilities in accordance with the quality requirements [IR Art. 8 (3)].
See ***Quality requirements***

Quality of a pharmacovigilance system
All characteristics of the pharmacovigilance system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.
See also ***Pharmacovigilance system, Quality system of a pharmacovigilance system***

Quality planning
Establishing structures and planning integrated and consistent processes [Art. 8(3) of IR 520/2012].
This applies for the purpose of fulfilling quality requirements.
See also ***Quality requirements***

Quality requirements
Those characteristics of a system which are likely to produce the desired outcome, or quality objectives.
See also ***Pharmacovigilance system, Quality system of a pharmacovigilance system***

Quality system of a pharmacovigilance system
The organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management [IR Art. 10 (2)].
The quality system is part of the pharmacovigilance system.
See also ***Pharmacovigilance system, Quality of a pharmacovigilance system***

Reference safety information
In periodic benefit-risk evaluation reports for medicinal products, all relevant safety information contained in the reference product information (e.g. the company core data sheet) prepared by the marketing authorisation holder and which the marketing authorisation holder requires to be listed in all countries where it markets the product, except when the local regulatory authority specifically requires a modification (see Annex IV, ICH-E2C(R2) Guideline).
It is a subset of information contained within the marketing authorisation holder's reference product information for the periodic benefit-risk evaluation report. Where the reference product information is the company core data sheet, the reference safety information is the company core safety information (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Company core data sheet, Company core safety information***

Registry
An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

Risk management plan (RMP)
A detailed description of the risk management system [see Art. 695 (28)[1] b) of Law 95/2006, as amended].
To this end, it must identify or characterise the safety profile of the medicinal product(s) concerned, indicate how to characterise further the safety profile of the medicinal product(s)

concerned, document measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation [Art. 30 of IR 520/2012].
See also ***Risk management system, Risk minimisation activity***

Risk management system
A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions [Art. 695 (28^1) a) of Law 95/2006, as amended].

Risk minimisation activity; synonym: Risk minimisation measure
A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine, or to reduce its severity should it occur. (see Annex IV, Guideline ICH-E2C(R2)).
These activities may consist of routine risk minimisation (e.g. product information) or additional risk minimisation activities (e.g. healthcare professional or patient communications/educational materials) (see Annex IV, Guideline ICH-E2C(R2)).

Risk-benefit balance
An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (Art. 695 (29) of Law 95/2006, as amended), i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health [Art. 695 (28), first point of Law 95/2006, as amended]).
See also ***Risks related to use of a medicinal product***

Risks related to the use of a medicinal product
Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment [Art. 695(28) of Law 95/2006, as amended].

Safety concern
An important identified risk, important potential risk or important missing information (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Important identified risk and Important potential risk, Important missing information***

Serious adverse reaction
An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [Art. 695 (11) of Law 95/2006, as amended].
"Life-threatening" in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).
Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic

bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).
Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
See also ***Adverse reaction***

Signal
Information arising from one or multiple sources, including remarks and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)].
For the purpose of monitoring data in the EudraVigilance database, only signals related to an adverse reaction is considered [IR Art 19(1)].
For the purpose of Section 16.2 of the periodic benefit-risk evaluation report, signals relate to adverse effects (see Annex IV, ICH-E2C(R2) Guideline).
See also ***Validated signal, Newly identified signal, Closed signal, Ongoing signal, Signal management process, Adverse reaction***

Signal management process
Includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [IR Art 21(1)].
It therefore is a set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks causally associated with an active substance or a medicinal product or whether known risks have changed.
See also Signal validation

Signal validation
Process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, therefore justifying further analysis of the signal [see Annex IV, Guideline ICH-E2D].
See also ***Validated signal***

Solicited sources of individual case safety reports
Organised data collection systems, which include clinical trials, registries, post-authorisation named - patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance. For the purpose of safety reporting, solicited reports should not be considered spontaneous but classified as individual case safety reports from studies and therefore should have an appropriate causality assessment by a healthcare professional or the marketing authorisation holder (see Annex IV, ICH-E2D).
See also ***Clinical trial, Post-authorisation safety study, Non-interventional trial***

Spontaneous report, synonym: Spontaneous notification
An unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation (e.g. the World Health Organization, a regional centre, a poison control centre) that describes one or more adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme (see Annex IV, ICH-E2D).
In this context, an adverse reaction refers to a suspected adverse reaction.

Stimulated reporting can occur in certain situations, such as after a direct healthcare professional communication (DHPC), a publication in the press or questioning of healthcare professionals by company representatives, and adverse reaction reports arising from these situations are considered spontaneous reports (see Annex IV, ICH-E2D), provided the report meets the definition above. Reporting can also be stimulated by invitation from patients' or consumers' organisations to their members. Reporting made in the context of early post-marketing phase vigilance (EPPV), e.g. in Japan, is also considered stimulated reporting.
*See also **Adverse reaction***

Stimulated reporting
See Spontaneous report

Substance
Any matter irrespective of origin which may be human (e.g. human blood and human blood products), animal (e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products), vegetable (e.g. micro-organisms, plants, part of plants, vegetable secretions, extracts), chemical (e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis) [Art. 695 (2) of Law 95/2006, as amended].

Summary of product characteristics (SmPC)
Part of the marketing authorisation of a medicinal product setting out the agreed position of the product as distilled during the course of the assessment process which includes the information described in Art. 708 of Law 95/2006. It is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in accordance with the summary of product characteristics (based on A Guideline on Summary of Product Characteristics, Volume 2C of the Rules Governing Medicinal Products in the EU).

Target population (treatment); synonym: Treatment target population
The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindication(s) in the authorised product information.

Traditional herbal medicinal product
A herbal medicinal product that fulfils the conditions laid down in Art. 714 (1) of Law 95/2006, as amended, i.e.
(a) it has (an) indication(s) exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;
(b) it is exclusively for administration in accordance with a specified strength and posology;
(c) it is an oral, external and/or inhalation preparation;
(d) the period of traditional use as laid down in Article 716 (1)(c) has elapsed;
(e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience [Art. 695 (30) and Art. 714 (1) of Law 95/2006, as amended]. Regarding (d), the product must have been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU (see Art. 716 (1) c) and European Commission Questions & Answers Document on Registration of Traditional Herbal Medicinal Products, 2011).
*See also **Herbal medicinal product***

Unexpected adverse reaction
An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics [Art. 695 (12) of Law 95/2006, as amended][7].

This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SmPC is that authorised by the competent authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a CHMP opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.
See also ***Summary of product characteristics***

Upper management
Group of persons in charge of the highest executive management of an organisation.
Membership of this group is determined by the governance structure of the organisation.
While it is envisaged that the upper management usually is a group, the head of the organisation is the one person at the top of the organisation with ultimate responsibility for ensuring that the organisation complies with relevant legislation.

Valid individual case safety report
See ***Individual case safety report***

Validated signal
A signal where the signal validation process of evaluating the data supporting the detected signal has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal [based on IR Art 21 (1)].
See also **Signal**

[7] For investigational medicinal products, an unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. the investigator's brochure for an unauthorised investigational product or the summary of product characteristics for an authorised product) [Order of the Minister of Health No. 904/2006, Art 2(p)]